Design: Development of Potent, Selective, and Stereospecific Ligands for the 5-HT_{1A} Receptor," J. Med. Chem., 1988, vol. 31, pp. 1087-1093, Supplementary Mat. Pp. 32-34 ("Hibert").

Applicant has cancelled each of these claims and submitted a replacement set of claims 69-90. Applicant thus respectfully traverses the Examiner's rejections as moot, and Applicant also traverses the rejections with respect to the newly added claims.

1. The Claimed Invention

The subject matter that was claimed by claims 22-38, 63-66 and 68, and which is similarly claimed by claims 69-90, is fully supported and made clear by the specification as filed. As claimed by claim 69, for example, the invention is directed to a computerized method of identifying a molecular feature set that is likely to be responsible for a given activity, based on a set of input data that represents molecules and that defines respectively for each molecule a molecular structure and an activity characteristic.

The method involves (i) establishing for each molecule a respective description, by comparison of the molecule's molecular structure to a set of molecular substructure keys, (ii) grouping the molecules based on similarity of their respective descriptions, so as to define groups of structurally similar molecules, (iii) selecting at least one of the groups of structurally similar molecules based on an extent to which the molecules in the selected group have activity characteristics reflecting the given activity, (iv) for each of the at least one selected group, identifying at least one molecular feature set common to all of the molecules in selected group,

As another example, claim 84 provides for applying this process iteratively. In particular, claim 84 provides for adding at least one identified molecular feature set as a new substructure

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key in the set of molecular substructure keys, and then repeating the functions of establishing descriptions, grouping molecules, selecting at least one group, and identifying a substructure common the molecules in the group.

Claims 22-38 and 63-65 used the term "pharmacophore" to describe a molecular feature set that is likely to be responsible for a given activity (*see* the specification, at page 5, lines 7-23); the new claims mean the same thing. Further, claims 22-38 and 63-65 called for "producing" or "establishing" a pharmacophore; the new claims call for "identifying" a pharmacophore, which is the same thing. (The Examiner noted in the Office Action that "producing" a pharmacophore seemed to involve physical production of a chemical structure. However, a reading of the specification together with the words of the claim makes clear that "producing" a pharmacophore means establishing the mechanism model, i.e., establishing or identifying what the molecular feature set is that is likely to be responsible for a given activity. (*Id.*))

2. Response to § 112 Rejections

a. Order of Steps

The Examiner first rejected claims 22-23, 31-32, 63-66 and 68 for failing to specify an order of steps. In particular, the Examiner noted that that the claims provide for output of data but do not recite an input of data.

Applicants submit that the function of inputting data into a computer is not necessarily part of Applicant's claimed invention (through it may be, depending on the claim). The existence

the data into the computer. And Applicant submits that the claims as filed were abundantly clear

in this regard. Further. Applicant notes that claims 63 and 65 expressly recited that an "input set of data representing a set of molecules" was analyzed.

Nevertheless, in the new claims, Applicant has expressly recited what was previously inherent, namely, that the claimed invention operates on "input data" or that input-data is received into a computer.

b. Relationship Between Preamble and Body

The Examiner next rejected claims 23-38 on grounds that the recited steps did not accomplish what the preamble recited. In particular, the Examiner noted that the preamble of these claims called for "producing" a pharmacophore but that the steps call for designing a pharmacophore. As noted above, producing a pharmacophore amounts to establishing or identifying what the pharmacophore is, as was recited in the preamble and body of each of claims 22-38 and 63-65 and as recited in the preamble and body of each of new claims 69-90. So Applicant submits that the preamble and body of each claim was and is consistent.

c. Meaning of "Pharmacophore"

The Examiner next rejected claims 22-38 on grounds that they used the term "pharmacophore" in their preambles. The Examiner did not understand what was meant by the term "pharmacophore." As noted above, the specification as filed defines the word "pharmacophore" as used in claims 22-38. (*See, e.g.*, specification, at page 5, lines 18-20 ("refer to the mechanism by which molecules in the library interact with a specified target or the mechanism by which molecules evidence any other activity.")) The new claims include that

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d. Meaning of "cooperatively"

The Examiner next rejected claims 22 and 23 on grounds that the claims used the term "cooperatively" to describe the scenario where molecules in a group had activity characteristics reflecting a given activity. The new claims exclude the word cooperatively, using other language instead to say the same thing. So this rejection is moot.

e. Having a Percent of Molecules with a Given Activity

The Examiner next rejected claims 26 and 35 on grounds that the claims recited, "selected group contains at least a predetermined percent of molecules having said particular activity characteristic." Continuing, the Examiner explained that "the selected group claimed was already clustered together by the parameters for clustering being the said particular activity." (*See* the Office Action, at page 3, lines 22-23.)

With all due respect, that is not what was recited in claim 26 or 35 (or their parent claims). Claim 26, for instance, depended from claim 24. Claim 24 recited that the molecules were grouped based on similarity of their respective descriptions. Claim 24 did not recite that the molecules were grouped based on their activity. According to the presently claimed invention, molecules are grouped (*e.g.*, clustered) based on similarity of their descriptions (keyed to *structure*), and a group is selected based on the activity characteristics of the molecules in the group. In turn, as recited in claims 26 and 35 (and as now claimed in claim 73), the selected group can be a group in which a predetermined percent of molecules have an activity characteristic reflecting a given activity. These claim elements are clear and definite.

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f. Clustering Along a Dimension Related to Activity

The Examiner next rejected claim 30 on grounds that it used the phrase "along a dimension related to the activity characteristics." Applicant has cancelled claim 30 and has not expressly included that language in the new claims. Therefore, this rejection is now moot.

Note, however, that the specification also provides for the *possibility* that molecules can be grouped based on *both* structure and activity, and that molecules can be grouped along a dimension related to activity characteristics. In canceling claims 29 and 30 and adding the new claims, Applicant does not intend to remove from the scope of any claim the possibility that molecules may be grouped based on both structure and activity, or the possibility that molecules may be grouped along a dimension related to activity, unless a claim expressly excludes such a feature.

g. Identifying a Pharmacophore Based on How Much the Pharmacophore Participates in Defining Discriminating Features of a Selected Group

The Examiner next rejected claims 22 and 32 on grounds that the claims called for identifying a common subset of features based at least in part on how much the subset of features participated in defining the discriminating features of the group. In this regard, the Examiner expressed concern about the use of the phrase "a measure of how much," as though a mathematical calculation were being applied to a chemical structure. Applicant has cancelled these claims. Therefore, the rejection is now moot.

Note, however, that the specification discusses this element. (For instance, the [illegible] the number of times each atom is included in a substructure key of hotspot in a SOM map, and so forth. (*See* specification, at page 30, line 25 - page 34, line 15.)) In canceling these claims,

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Applicant does not intend to exclude the possibility that this element could be included within the scope of any claim that does not expressly exclude the element.

3. Response to § 102 Rejection

The Examiner next rejected claims 22-38, 63-66 and 68 under 35 U.S.C. § 102(b) as being anticipated by Hibert.

Under M.P.E.P. § 2131, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Applicant respectfully traverses the rejection of claims 22-38, 63-66 and 68, because Hibert does not disclose or suggest each and every element of any one of these claims. Further, Applicant has cancelled claims 22-23, 63-66 and 68. Therefore, the rejection of these claims over Hibert is now moot.

Applicant also submits that pending claims 69-90 are patentably distinct over Hibert. For example, with respect to claims 69-82, Hibert does not teach the claimed method of (i) establishing a description of each molecule by comparison of the molecule's structure to a set of substructure keys, (ii) grouping the molecules based on similarity of their respective descriptions, (iii) selecting at least one of the groups based on an extent to which the molecules in the group have activity characteristics reflecting a given activity, (iv) identifying a molecular feature set common to all molecules in the selected group, and (v) outputting data indicating the molecular feature set.

[illegible] method that further includes the function of adding an identified feature set as a new substructure key in the set of substructure keys, and the function of repeating the steps of (i) establishing

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descriptions based on comparison to the set of structure keys, (ii) grouping based on similarity of descriptions, (iii) selecting based on extent to which molecules reflect the given activity, and (iv) identifying a molecular feature set (as more specifically recited in claim 84).

In the Office Action, the Examiner asserted that Hibert demonstrates establishing molecular descriptions based on structural features. However, Applicant claimed more than that; Applicant claimed doing this based on a comparison of molecular structure to a set of descriptors (i.e., substructure keys). And Hibert does not disclose establishing a description of each molecule by comparison of the molecule's structure to a set of substructure keys as claimed. In fact, Hibert's rote analysis of molecules in search of a common aromatic ring and nitrogen atom reference pair (which the Examiner points to in support of this rejection) does not amount to a process of establishing a description of each molecule as claimed.

In addition, the Examiner asserted that Hibert demonstrates selecting a group of molecules based on similar descriptions. However, Applicant claimed more than that; Applicant claimed a function of selecting a group of molecules that have similar descriptions and that cooperatively represent a particular activity characteristic. I.e., molecules are grouped based on similarity of their descriptions and a group reflecting a particular activity characteristic is selected.

And Hibert does not disclose or suggest selecting a group of molecules based on similar *structure* of the molecules. Rather, at best, Hibert discloses selecting a group of molecules based on the common *activity* of the molecules. In particular, Hibert selects four molecules that have a [illegible] recognition site). Hibert *then assumes* that, because the molecules have similar activity, the probably contain a common pharmacophore.

Further, the Examiner stated that Hibert anticipates "a new descriptor arrangement." (*See* the Office Action, at page 5, lines 9-12.) Applicant is not certain what the Examiner meant by this statement. But Applicant believes the Examiner might have been arguing that Hibert teaches the iterative process as claimed -- namely, the process of establishing a pharmacophore (a molecular feature set), adding that pharmacophore as a new substructure key in a set of substructure keys, and then repeating the claimed process, including establishing a description of each molecule based on comparison between the molecule's structure and the set of substructure keys. If that is what the Examiner meant, Applicant strongly disagrees.

Hibert does not disclose or suggest the function of learning and using a new key as presently claimed (in claim 84, for instance). First, Hibert does not teach a process of establishing a description of a molecule. Therefore, Hibert cannot possibly teach a process of using a newly learned key as a basis to establish a description of a molecule. Second, the fact that Hibert identifies a pharmacophore is not the point. Applicant does not claim to have invented the idea of merely discovering pharmacophores; Applicant's invention is more specific than that. And Hibert fails to teach what Applicant has claimed.

Still further, the Examiner asserted that Hibert teaches clustering of data representing molecules. In this regard, the Examiner pointed to Hibert's supplementary material. With all due respect, however, Applicant submits that Hibert does not disclose clustering of data representing molecules. In fact, all Hibert's supplementary material provides is a chart listing atomic coordinates of putative receptor-bound conformations for methiothepin, propranolol, buspirone

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Because Hibert fails to disclose or suggest all of the elements of any of the presently pending claims, Applicant submits that Hibert fails to anticipate any of the claims under 35 U.S.C. § 102. Therefore, Applicant respectfully requests allowance of all of the pending claims.

3. Information Disclosure Consideration

In the Office Action, the Examiner also indicated that several of the publications listed on the information disclosure statement filed July 12, 1999, have not been considered. Applicant respectfully requests the Examiner to consider those publications, which Applicant submitted for consideration. Applicant does not believe that the form of the date should preclude the Examiner from considering these references.

Some of the publications were printouts from the World Wide Web, and the Examiner declined to consider those publications because Applicant referred to the date of printout as the publication date. Applicant requests the Examiner to consider those publications, using the date of printout of each document as the "at least as early as" date of publication, i.e., considering that each such web printout was published at least as early as the date of printout.

Another publication was an article by Barnard, which the Examiner declined to consider because Applicant referred to the "received date" as the date of publication. Applicant requests the Examiner to consider that article, using as the date of publication the date of presentation indicated in the first footnote of the article.

Applicant also respectfully requests the Examiner to confirm in the next Action that the [illegible] these references [illegible] exist in this regard. For the Examiner's convenience, Applicant encloses another copy of the Form PTO-1449 that Applicant filed on July 12, 1999.

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Applicant invites the Examiner to call the principal attorney of record, Lawrence H. Aaronson, at (312) 913-2141, if any additional issues exist.

Respectfully submitted,

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